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Relationship between diet and ankylosing spondylitis: a systematic review

Running head: Role of diet in ankylosing spondylitis

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Abstract

The question of whether diet plays a role in the onset of Ankylosing spondylitis (AS), or can affect the course of disease is an important one for many patients and health care providers.

The aims of the study were to investigate whether: 1) patients with AS report different diet to those without; 2) amongst patients with AS diet is related to severity; 3) persons with particular diets are less likely to develop AS; 4) specific dietary interventions improve symptoms of AS.

The review was conducted according to PRISMA guidelines. Medline, Embase, Cochrane Library and reference lists of relevant articles were searched. Two authors independently selected eligible studies, assessed quality of included trials and extracted data.

Sixteen studies (9 observational and 7 intervention) were included in the review. Due to the heterogeneity of study designs and analyses, the results could not be pooled.

Evidence on a possible relationship between AS and diet is extremely limited and inconclusive due to the majority of included studies being small, single studies with moderate to high risk of bias and insufficient reporting results.

Key words: ankylosing spondylitis, rheumatic disease, diet, nutrition, systematic review

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease with estimated prevalence per 10,000 of 23.8 in Europe, 16.7 in Asia, 31.9 in North America, 10.2 in Latin America and 7.4 in Africa (1). AS adversely affects patients in terms of symptoms such as pain and fatigue leading to impaired function and diminished quality of life (2,3). Despite the development of biologic therapy, which has revolutionised the treatment of AS (4), many patients explore complementary treatments such as dietary therapy.

There is overwhelming evidence of the importance of diet in the aetiology of a wide range of diseases such as rheumatoid arthritis (RA), cardiovascular disease and cancer (5,6,7). An examination of dietary patterns in a large cohort of nurses in the United States found that dietary patterns characterised by high intakes of fruit, vegetables, legumes, whole grains, poultry, and fish, was associated with a reduced risk of RA. In contrast, dietary patterns typical of industrialised countries (high intake of red meats, processed meats, refined grains, French fries, desserts and sweets, and high-fat dairy products) was associated with an increased risk of RA (8). A meta-analysis of placebo-controlled trials in patients with RA reported that that dietary fish oil has a modest effect in reducing tender joint count and morning stiffness (9), an effect attributed to the anti-inflammatory mechanism of omega-3 polyunsaturated fatty acids.

It has been suggested (10,11,12,13) that low starch diet leads to lower AS disease activity and that *Klebsiella pneumoniae,* which can be influenced by starch consumption, is a triggering factor involved in the initiation and development of AS (12).

Although some publications have considered the evidence linking AS with diet (14,15,16,17,18,19), there have been no systematic evaluations of the evidence.

The objectives of this systematic review were to investigate whether:

1) patients with AS report different diet to those without.

2) amongst patients with AS diet is related to severity.

3) persons with particular diets are less likely to develop AS.

4) specific dietary interventions improve symptoms of AS.

Materials and methods

The review protocol was registered with PROSPERO (20), an international register of systematic reviews (registration number: CRD42015026699). We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21).

Literature search strategy

The search terms relating to AS (AS, Spondyloarthropathy, Spondylitis, spondyloarthritis) were combined with terms relating to diet (diet, nutrition, food, food habits, nutritional status, vitamins, antioxidants, fatty acids, carbohydrates, dietary protein, calcium, fish oils, fruit, vegetables, micronutrients) to find articles published up to August 2016 in Embase and Medline. Additionally, two journals (Annals of the Rheumatic Diseases and Annual Review of Nutrition) were searched manually from 2010 to 2015. The references of retrieved manuscripts were screened for further relevant papers.

Inclusion and exclusion criteria

We included all observational studies on humans (cross-sectional, cohort, case-control and case series studies) but we excluded case reports. We also excluded case series with small number of study participants (<5). Uncontrolled treatment outcome studies and Randomized controlled trials (RCT) were also included. Participants had to be at least 18 years old. We considered studies published in English that evaluated presence of AS (or axial spondyloarthritis (axSpA) using established criteria or clinical diagnosis, included assessment of diet and quantified an association between AS (or axSpA) and diet. In this review, we did not consider alcohol consumption.

Data extraction

Two independent reviewers screened the title and the abstract of each study following the inclusion criteria. If disagreement occurred between the two reviewers, a third reviewer was consulted.

For eligible studies, data extraction was performed by two independent reviewers using a specially designed data collection form.

Assessment of study quality

We used the Scottish Intercollegiate Guidelines Network (SIGN) methodology checklists to assess the quality of individual studies (22). Two reviewers conducted the quality assessment independently. If disagreement occurred, a third reviewer was consulted.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence (23,24).

Results

Search results

The search of the databases resulted in 582 publications (Figure 1). After the removal of irrelevant papers (n=512) and duplicates (n=18) and having found additional 10 papers from other sources including searching the references of full text papers, 58 full text published papers, two letters and five conference abstracts were considered. After further consideration, three abstract were removed because they did not include the necessary information and 46 full text articles were removed because they did not report AS (n=3), did not look at relationship between AS and diet (n=2), included children (n=1), very small sample of AS patients (n= 4), contained case report (n=3), did not report information on diet (n=1), was in Chinese language (n=1), did not report diet (n=25), did not report information on AS (n=2), were non-systematic reviews (n=3) and thesis (duplicate publication, n=1). There were total of 16 studies included in the review, ten of which were full text papers (25,26,27,28,29,30,31,32,33,34), two were letters (35,36), two studies were summarised in review articles (37,38) and two were conference abstracts (39,40).

Description of the included studies and participants

Multiple studies were conducted in Sweden (27,32,33,34) and United Kingdom (37,38,28), and individual studies in Norway (25), Belgium (35), France (26), Australia (29), New Zealand (30), China (31), Portugal (39) and Turkey (40) (Table 1, Appendix 1) and were published between 1991 (25) and 2014 (39,34,40). Seven of the included studies were case series (25,26,29,32,33,39,40); three were treatment outcome studies with all the participants receiving intervention (35,37,38), three were randomised clinical trials (27,28,30), one was case-control study (34) and one study investigated gene-environment interaction using a case-only design (31). All of the studies were conducted in hospital setting (Table 1, Appendix 1) except one (28) which recruited participant *via* a web site. Eight studies only reported inclusion criteria while three others only reported exclusion criteria.

Participation rate was reported by three studies describing case series (25,29,32) (range 46%-93%) and one case-control study (34) (89%). None of the treatment outcome studies reported follow-up rate, while follow up rate in RCTs was between 65% (28) and 100% (30). Minimum duration of follow up was 3 months and maximum 10 months (Table 1, Appendix 1).

Study size ranged from 12 (39) to 293 participants (26). Among 11 studies that reported gender distribution, females comprised between 19% (31) and 38% (27). Among 10 studies that reported age distribution, mean age ranged between 30 (31) and 50 (32) years. Only eight studies specified disease duration with mean ranging between 9 (30) and 27 (32) years (Table 1, Appendix 2).

Among nine studies that reported diagnostic criteria for AS the most common was Modified New York criteria (41) reported by five studies (29,31,32,33,34), the European Spondylarthropathy Study Group (ESSG) (42) reported by four studies (35,26,30,40), the Amor criteria (43) by two studies (26,40) and the Assessment of Spondyloarthritis International Society (ASAS) classification criteria (44) by one study (40) (Table 1, Appendix 2).

The following criteria were used to measure disease activity: the Bath Ankylosing Disease Activity Index (BASDAI) (45) (9 studies), Bath Ankylosing Functional Index (BASFI) (46) (7 studies), Bath AS Patient Global Score (BASG) (47) (3 studies), AS Quality of Life (ASQoL) index (48) (2 studies), ASAS (49) and ASAS20 (50) (one study), SF-36 (51) (2 studies), erythrocyte sedimentation rate (ESR) (5 studies), C-reactive protein (CRP) (5 studies), aggravation of symptoms (25,32), change from baseline (35), VAS (36,30) and medication requirement (25,27) (Table 1, Appendix 2).

Availability of information on diet and nutrition

In the observational studies assessment of diet was conducted using questionnaire (25,31,32,33,34) with three studies (32,33,34) using a validated, 84-question semiquantitative food frequency questionnaire (FFQ) (52,53). Other methods used were food diary (39), face-to-face interview (40), interview with a dietician (26) and telephone survey (29) (Table 1, Appendix 2).

Studies examined different types of food and nutrients in relation to AS, most commonly the consumption of starch, dairy and different types of diet (Table 2, 3, Appendix 3).

Quality of studies

As studies included in this systematic review had different designs, their quality was assessed separately as case series (Appendix 4), treatment outcome studies (Appendix 5), case-control study (Appendix 6) and RCTs (Appendix 7).

The quality could not be fully assessed in studies published as abstracts (39,40), letters (35,36) or described in reviews (37,38). Overall GRADE quality of evidence was low or very low (Table 2, 3) with only two studies, both RCTs, fully satisfying the quality criteria (28,30). In studies of

intervention, compliance was assessed by questioning the participants about adherence to diet (35,37), by counting the remaining capsules (27), by asking the participants to report on the number of study capsules that they had taken during the previous week (28) or by asking the participants to return all study drug containers for weighing (30).

Most studies, especially more recent, used modern statistical methods and investigated the effects of potential confounding factors such as age, gender, smoking and body mass index (BMI) (Appendix 8).

None of the studies investigated data to answer whether persons with particular diets are less likely to develop AS (Objective 3).

Objective 1: Comparison of diet in patients with AS and those without AS

Only one case-control study (34) investigated whether diet differs among AS patients compared to persons without AS (Table 2-3). The calculated energy intake was significantly higher among AS patients compared to controls (1,940 vs. 1,819 kcal, P<0.05). The difference in the calculated energy intake remained after adjustments for physical activity level, weight, sex and age. Apart from differences which were not significant, i.e. a lower intake of monounsaturated fats (P=0.07) and total fat (P=0.07) among the patients, there were no other differences in diet (consumption of dairy products, fish, meat, fruits and vegetables) compared with controls (Appendix 10-13).

Ge et al (31) performed an association study examining gene-environment interaction between IL-1F7 gene polymorphisms and measures of dietary exposure. There was an interaction with type of cooking oil with an increased risk for cooking using half plants - half animal fats (OR 4.27, 95% CI 1.59-11.48, P = 0.004). Interaction between IL-1F7 alleles and other factors such as salt, meat or vegetable consumption in AS patients was not statistically significant (all P>0.05) (Table 2-3; Appendix 12-14).

Objective 2: Diet and severity of AS (observational studies)

Overall, evidence on diet and AS severity was limited, and we were unable to perform a meta-analysis due to lack of report of data, diversity in outcome and definition of exposure.

Haugen et al (25) reported that 78% of AS patients believed that diet influenced symptoms of their disease and one third of the patients reported worsening symptoms after intake of certain foods with 35% mentioning increased swelling of the joints. Foods most frequently implicated were meat, coffee, sweets, sugar, chocolate, citrus fruits and apples. Sixteen percent of the AS patients had been through a fasting period on their own initiative with the majority reporting less pain, less stiffness and less joint swelling. Twenty-two percent of patients with AS in an attempt

to alleviate disease symptoms had previously tried diets such as lactovegetarian or vegan diets (Appendix 16).

Of the four studies reporting data on the relationship between food high in starch and AS severity (26,32,39,40), two (26, 32) were conference abstracts (Appendix 9, Table 2). While one study (39) reported a significant association of daily starch intake with the BASDAI, BASFI and BASG, other studies did not find an association between consumption of food high in starch and BASDAI (26,40). There was no association of daily starch intake with the SF-36, CRP or ESR (39). A small proportion of patients (1.8%) reported aggravation of symptoms associated with food rich in flour (32). Silva (39) reported that average starch intake was significantly, positively associated with BASDAI, BASFI, and BASG but not with SF-36, CRP or ESR. The linear regression showed increases of 3%, 3.9% and 2.9% in BASDAI, BASFI and BASG scores, respectively, by milligram of ingested starch. The authors concluded that higher intake of starch was related to increased disease activity and greater functional impairment.

Three studies that reported data on the relationship between consumption of dairy products and AS (32,26,40) did not find any association with BASDAI (Table 2, Appendix 10). One study that reported case series (32) did not find an association between consumption of fish and dietary omega-3 fatty and BASDAI (Table 2, Appendix 11).

Sundström et al. (32) reported in a study of 111 patients that seven patients experienced aggravated arthralgia or AS symptoms associated with a particular foodstuff, most commonly vegetables/fruits (n=2) or food rich in flour (n=2) (Appendix 9, 12, Table 2).

Taşpınar et al (40) reported no association between consumption of salt and fast food, and the BASDAI. Claudepierre et al (26) reported that among dietary factors the frequency of meals taken out of home was the only variable related (negatively) to disease activity. Mean (SD) BASDAI score among those eating out of home twice per week or less was 5.1 (2.1) compared to 4.1 (2.1) among those who ate out of home more than twice per week ($P<0.001$) (Table 2, Appendix 14).

Sundström et al. (33) reported that there was no correlation between dietary fat intake and disease activity assessed by BASDAI. ESR correlated negatively with dietary total polyunsaturated fatty acids (PUFA) and omega-3 long-chain polyunsaturated fatty acids (LCPUFA) ($rs = –0.25$ and $rs = –0.27$, respectively, $P<0.05$). While no correlation between dietary intake and disease activity, as measured by BASDAI, was found overall Amongst women, there were negative correlations between the percentage energy intake derived from

fat and saturated fats with BASDAI (rs=−0.43, P<0.05 and rs=−0.50, P<0.01, respectively) (32) (Appendix 8, Table 3).

Sundström et al. (32) stated that thirty-two patients (29%) reported that they had consumed herbal products, multivitamins and other food supplements during the preceding 2 weeks. The most common were omega-3 (n=13; median intake 1g/day), multivitamin and/or multimineral (n=12), and iron (n=4) supplements. (Table 2, Appendix 15).

Chatfield et al (29) reported that 82.7% of AS patients used complementary and alternative medicine (CAM) and of these patients 16 (25.8%) were using seven or more types. Forty-four AS patients (72.1%) reported a form of dietary CAM among whom 28 (37.4%) were using multiple types at the time of study. The most common dietary CAMs were fish oil (26.7% of the study population), green tea (25.3%), vitamin supplements (24.0%) and glucosamine (21.3%). Of a total of 89 dietary CAM only 10 were initiated by a CAM practitioner and 50 were reported to be of little or no benefit. There was no significant difference between dietary CAM users and non-users across a range of disease indices (ESR, CRP, BASDAI, BASFI, ASQoL or BASG) (Table 2, Appendix 15).

Objective 4: Dietary interventions and symptoms of AS

Appelboom et al. (35) investigated, in a single-arm intervention study of 25 patients, whether a diet that excluded dairy products, was beneficial for the course of disease. The results at six weeks of follow up showed relatively good compliance to the diet (72%). Amongst participants, 52% reported good improvement of whom 62% could discontinue their NSAID therapy. When follow up of the responders was carried out, 80% of 15 patients three months, all 10 patients at six months and 89% of 9 patients at nine months were satisfied and had continue the dietary regime. The authors reported that six patients were still observing the diet after two years of follow up and remained free from any other therapy (Table 2, Appendix 10).

Ebringer and Wilson (37) in a single-arm intervention study of a low starch diet in 36 AS patients reported a significant reduction (P<0.001) in ESR levels over a 9-month period. The authors also reported that the majority of the participants reported that the severity of symptoms declined and in some cases disappeared. Some patients noticed a decrease in requirement for NSAIDs, however no precise figures were reported. The authors reported that they treated over 450 AS patients from 1983 onwards and that over half of these patients did not require any medication at follow up. Ebringer et al (38) reported a decrease in ESR in a single-arm intervention study of low starch, high protein, high vegetable and fruit diet with 10 months follow up, however precise figures were not reported (Table 2, Appendix 9).

Sundström et al (27) reported a randomised trial of high- versus low- dose fish oil with 21 weeks follow up with participants blinded to the dose. At the end of the study there was a statistically significant decrease in BASDAI scores (p=0.038) in the high-dose group and a statistically significant increase in ESR in the low-dose group (p=0.027), but no other significant differences. However, there was not a statistically significant difference comparing the high-dose and low-dose groups (Table 2, Appendix 11).

A small uncontrolled intervention study investigated the effects of giving *Lactobacillus acidophilus* and *Lactobacillus salivarius* daily for 4 weeks in 18 patients with quiescent ulcerative colitis but active SpA (36). Significant improvements were seen in BASDAI (reduction in mean (SD) from 5.8 (1.5) at baseline to 4 (1.8) at follow up, P<0.05) and pain VAS (reduction from 58.1 (16.8) to 41.5 (14.3), P<0.05). However, neither of two RCTs found a significant effect of probiotic supplementation on AS outcome such as disease activity, function, wellbeing, BASDAI, BASFI, pain levels, CRP or ASQoL (28,30).

We did not perform a meta-analysis due to diversity of outcomes and types of probiotic supplements (Table 2, Appendix 15).

Discussion

This is the first systematic review to examine the association between AS and diet. It has showed that only a few, relatively small, and mainly observational studies have been conducted in this field. From the 16 articles included in the review, there is little evidence that aspects of diet influence the severity of AS or are part of its aetiology. Specifically, there is no evidence that reduction in starch intake, exclusion of dairy products, fish and fish oil consumption and probiotic supplementation reduce susceptibility to AS or diminish AS symptoms.

This review has many methodological limitations. Firstly, there is scarce literature on the topic and 6 out of 16 studies were not published as full reports and therefore limited data were available for data extraction. Several studies did not report the actual figures and results of the analysis. The studies included in this review vary extensively in design, AS diagnostic criteria, measures of disease severity, exposure measured, measurement instruments, intervention and duration of follow-up. Therefore, it was not possible to conduct a meta-analysis.

Although we limited our search to publications in English language, the studies included in this review were from ten countries. Most studies were conducted in hospital setting, except one study that used patient society website (28). The participation rate and way of selection the participants were not stated in the majority of the studies and therefore it is difficult to judge how representative

they were, limiting the generalizability of the findings. Most studies, especially more recent, used appropriate statistical methods and investigated the effects of potential confounding factors.

Retrospective assessment of dietary exposure may introduce recall bias. However observational studies included in this review seem to evaluate current dietary habits, except one study (29) which collected information on special diets and food avoidance in the past three months and one study (39) that used food diary over the five consecutive days. In addition, when assessing dietary risk factors in prevalent cases of AS, it is difficult to distinguish whether diet influences the development of AS or the course of the disease. It is also common for people to change their diets soon after the onset of disease, and therefore current diet may not actually represent past dietary intake. Validated FFQ was used in three observational studies from the same research group (32,33,34), and reproducibility was assessed in study by Haugen et al (25), however reliability and validity of the dietary data collected in other studies was not clear.

The majority of AS patients (78%) as well patients with other rheumatic diseases (rheumatoid arthritis (RA) 64%, juvenile rheumatoid arthritis (JRA) 88%, psoriatic arthropathy 71%, osteoarthrosis 65%) believe that diet influences their disease symptoms (25). This suggests that if diet is important it may influence the inflammatory process across rheumatic diseases.

Studies of AS and other rheumatic diseases report dietary interventions such as fasting, vegan diet and lactovegetarian diet (25,54). Clinical dietary therapy studies of AS have focused on some form of dietary elimination such as low starch diet (37) and diet that excludes dairy products (35).

Gut involvement in the pathogenesis of rheumatic diseases was proposed by Smith (55), and more recent studies investigated it further (54,56), suggesting that as the intestinal bacterial flora may be affected by diet, a diet which could influence the intestinal flora might have an effect on disease activity. *Klebsiella pneumoniae* was suggested as a trigger for AS and Crohn's disease based on molecular mimicry (12), and a low-starch diet was proposed as a means of reducing *Klebsiella* bacteria in the gut and hence further pathological damage (10,11,12,13). The gut microbiome can also be altered using probiotics, live bacteria and yeasts considered as having possible health benefits (57). Animal models have shown that *Lactobacillus casei* can reduce joint damage in mouse models of arthritis, while HLA-B27 transgenic rats have been shown to be less likely to have a relapse of colitis when given *Lactobacillus rhamnosus GG* (58). However while one uncontrolled study of probiotics (36) included in this review showed an improvement in BASDAI and VAS scores, two RCTs (28,30) did not confirm this association. Several small trials of probiotics in RA patients have reported marginal, non-significant beneficial effects (59,60,61)

on RA disease activity. A recent case-control study showed that breast feeding, which influences microbiota, reduces the risk of the development of AS (62).

Core set of recommendations for patients with AS proposed by Feldtkeller et al (19) advises a reduction in meat consumption, and increase in consumption of fish and vegetarian meals. In addition, it is recommended that sufficient vitamin D and calcium intake are important to prevent osteoporosis.

Conclusion

In this systematic review, we have determined, from a relatively small number of studies, that the evidence on the relationship between diet and AS is extremely limited and we have highlighted important methodological weaknesses in the studies reviewed.

Many AS patients believe that aspects of diet affect their symptoms and/or have altered their diets in attempt to improve symptoms. However, well-designed studies of dietary patterns and nutrients are required before any AS-specific recommendations could be made. Future prospective, population-based studies using validated dietary assessment methods should focus on dietary patterns that have been implicated in other inflammatory conditions, including cardiovascular disease, to determine whether diet plays a role in susceptibility to AS and AS severity.

Clinical and Research Consequences

- Information on relationship between diet and AS is extremely limited
- Evidence on a possible relationship between AS and diet is inconclusive
- There is need for large population-based epidemiological studies investigating the relationship between AS and diet

Conflict of interest

TVM reports grant from National Ankylosing Spondylitis Society (NASS), during the conduct of the study. HMA has nothing to disclose. EP has nothing to disclose. KG has nothing to disclose. JH has nothing to disclose. GJM reports grant from NASS, during the conduct of the study; and GJM is Chief Investigator of the British Society for Rheumatology (BSR) Biologics Register in Ankylosing Spondylitis. The BSR receives or has received funds for the conduct of this register from Pfizer, AbbVie and UCB.

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Figure legends

Figure 1. Flow diagram of study selection process for the systematic review on diet and ankylosing spondylitis (AS)

Table 1. Description of studies

Description	**N or (min, max) as appropriate**
Total	16
Publication year	1991, 2014
Country	
Norway	1
Belgium	1
United Kingdom	3
France	1
Sweden	4
Australia	1
New Zealand	1
China	1
Portugal	1
Turkey	1
Italy	1
Study type	
Observational	9
Case-control	1
Case series	8
Intervention	6
Uncontrolled treatment outcome	4
Randomised Clinical Trial (RCT)	3
Study size	12, 439
Gender	
% Females	19, 56
Not reported	4
Age (years)	30,50
Not reported	5
AS diagnostic criteria	
Modified New York	5
European Spondylarthropathy Study Group (ESSG)	4
Amor	2
Assessment of Spondyloarthritis International Society (ASAS)	1
Hospital diagnosis (not specified)	7
Measure of disease activity	
Bath Ankylosing Disease Activity Index (BASDAI)	9
Bath Ankylosing Functional Index (BASFI)	7
Bath AS Patient Global Score (BASG)	3
AS Quality of Life (ASQoL)	2
Assessment of Spondyloarthritis International Society (ASAS)	1
36-Item Short Form Health Survey (SF-36)	2
Erythrocyte Sedimentation Rate (ESR)	5
C-reactive protein (CRP)	5
Medication requirement	2
Aggravation of symptoms	1
Change from baseline	1
Visual Analogue Scale (VAS)	1
Assessment of diet	
Questionnaire	5
Interview	2
Telephone interview	1
Food diary	1
Intervention	7

AS ankylosing spondylitis;

Table 2. Summary of findings (type of food/diet)

Exposure	**Outcome**								
Food/ diet	**Patients with AS *vs* Controls**			**Dietary consumption and severity of AS**			**Dietary intervention and severity of AS**		
	Participants (studies)	Result	Quality of evidence (GRADE)	Participants (studies)	Result	Quality of the evidence (GRADE)	Participants (studies), follow-up	Result	Quality of evidence (GRADE)
High-starch food	-	-	-	405 (2) 12 (1) 12 (1) 111 (1)	-BASDAI: No association (no data) -ESR, CRP, SF-36: No association -BASDAI, BASFI, BASG: Sign. association -Symptom aggravation	Very low	110 (2), 9-10 months 36 (1), 9 months	Low starch diet: Sign. Reduction in ESR Symptom improvement (no data)	Very Low
Dairy products	77 AS / 307 Controls (1)	No sign. difference	Low	504 (3)	BASDAI: No association (no data)	Very low	25 (1), 9 months	Dairy excl. diet: Self-reported therapeutic effect	Very Low
Fish / fish oil	77 AS /307 Controls (1)	Fish consumption: No sign. difference	Low	111 (1)	Fish consumption: No association (no data)	Very low	18 (1), 21 weeks	High- *vs* low-dose fish oil: No sign. difference	Very Low
Meat and meat products	77 AS /307 Controls (1) 150 AS only (1)	-No sign. difference - Non-sign. gene IL-1F7 interaction	Low	404 (2)	BASDAI: No association (no data)	Very low	-	-	-
Fruit and vegetables	77 AS /307 Controls (1) 150 AS only (1)	-No sign. difference - Non-sign. gene IL-1F7 interaction	Low	111 (1)	Symptom aggravation	Very low	-	-	-
Probiotic supplements	-	-	-	-	-	-	18 (1), 4 weeks	-BASDAI, VAS: Sign. association - BASFI, ESR, CRP: No association	Low

							196 (2), 12 weeks	BASDAI, VAS, BASFI, CRP, ASQoL: No sign. difference compared to placebo	
CAM	-	-	-	75 (1)	BASDAI, BASFI, BASG, ASQoL, ESR, CRP: No association	Very Low	-	-	-
Cooking oil	150 AS only (1)	Sign. gene IL-1F7 interaction (half plants-half animal fat)	Low	-	-	-	-	-	-
Salt consumption	150 AS only (1)	Non-sign. gene IL-1F7 interaction	Low	100 (1)	BASDAI: No association (no data)	Very Low	-	-	-
Convenience food	-	-	-	293 (1) 100 (1)	BASDAI: No association with consumption of canned or frozen food (no data); Sign. inverse association with number of meals taken out of home BASDAI: No association with fast food consumption (no data)	Very Low	-	-	-

AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Disease Activity Index; ASQoL: AS Quality of Life; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; SF-36: 36-Item Short Form Health Survey; -BASDAI: Bath Ankylosing Disease Activity Index; BASFI: Bath Ankylosing Functional Index; BASG: Bath AS Patient Global Score; VAS: Visual Analogue Scale; GRADE: Grading of Recommendations Assessment, Development and Evaluation system

Table 3. Summary of findings (nutrients)

Exposure	Outcome					
Nutrient	**Patients with AS *vs* Controls**			**Dietary consumption and severity of AS**		
	Participants (studies)	Result	Quality of evidence (GRADE)	Participants (studies)	Result	Quality of evidence (GRADE)
Energy	77 AS /307 Controls (1)	Sign. higher in cases	Low	111 (1)	BASDAI: No association (no data)	Very Low
Protein	77 AS /307 Controls (1)	No sign. difference	Low	177 (2)	BASDAI, ESR, CRP: No association	Very Low
Carbohydrate	77 AS /307 Controls (1)	No sign. difference	Low	177 (2)	BASDAI, ESR, CRP: No association	Very Low
Fat	77 AS /307 Controls (1)	No sign. difference	Low	111 (1) 66 (1)	BASDAI: Sign association in women only BASDAI, ESR, CRP: No association	Very Low
Fibre	77 AS /307 Controls (1)	No sign. difference	Low	111 (1)	BASDAI: No association (no data)	Very Low
Saturated fatty acids	77 AS /307 Controls (1)	No sign. difference	Low	177 (2)	BASDAI, ESR, CRP: No association	Very Low
Mono-unsaturated fatty acids	77 AS /307 Controls (1)	No sign. difference	Low	-	-	-
Poly-unsaturated fatty acids	77 AS /307 Controls (1)	No sign. difference	Low	177 (2) 66 (1)	BASDAI, CRP: No association ESR: Sign. association	Very Low
Linoleic acid	77 AS /307 Controls (1)	No sign. difference	Low	66 (1)	BASDAI, ESR, CRP: No association	Very Low
Alpha-linolenic acid	77 AS /307 Controls (1)	No sign. difference	Low	66 (1)	BASDAI, ESR, CRP: No association	Very Low
Long-chain omega-3 fatty acids	77 AS /307 Controls (1)	No sign. difference	Low	177 (2) 66 (1)	BASDAI, CRP: No association ESR: Sign. association	Very Low

AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Disease Activity Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; GRADE: Grading of Recommendations Assessment, Development and Evaluation system

List of Appendices (For online publication)

Appendix 1. Description of the included studies

First author, Publication year	Country	Study type	Recruitment	Inclusion criteria	Exclusion criteria	Follow up (months)	Particip. rate
Haugen, 1991 (25)	Norway	Case series	Oslo Sanitetsforening Rheumatism Hospital and Department of Rheumatology, University Hospital of Tromsø	Age above 18 years	No information	N/A	46%
Appelboom, 1994 (35)	Belgium	Uncontrolled treatment outcome	Outpatient clinic	No information	No information	9	No information
Ebringer, 1996 (37)	United Kingdom	Uncontrolled treatment outcome	Middlesex Hospital, London	Active AS (ESR>15 mm/hr)	No information	9	No information
Claudepierre, 1998 (26)	France	Case series	Nine rheumatology departments throughout France	No information	No information	N/A	No information
Ebringer, 2006 (38)	United Kingdom	Uncontrolled treatment outcome	AS research clinic, Middlesex Hospital, London	No information	No information	10	No information
Sundström, 2006 (27)	Sweden	RCT	Hospitals of Gällivare and Kiruna	Active disease, age 18-70 years, having diagnosis of AS made by a rheumatologist	Treatment with methotrexate, etanercept or infliximab, pregnancy, active Crohn's disease, food intolerance to fish	5.3	Follow up rate 75%
Brophy 2008 (28)	United Kingdom	RCT	Internet link posted on NASS website	Age above 18 years, resident in UK, access to internet, diagnosis of SpA	Immunosuppressive disorder	3	Follow up rate 65%
Chatfield, 2009 (29)	Australia	Case series	Austin Spondylitis Clinic (AS referral centre), Melbourne	Satisfy modified New York criteria for AS	No information	N/A	92.6%
Sanges, 2009 (36)	Italy	Uncontrolled treatment outcome	Gastroenterology unit, Naples	Active SpA (BASDAI≥4), and quiescent ulcerative colitis according to UCDAI	No information	4 weeks	No information

Jenks 2010 (30)	New Zealand	RCT	Department of Rheumatology, Dunedin Hospital	BASDAI≥3, BASFI≥3, MASES≥2 or peripheral joint count ≥2	Pregnancy, age<18 years, diagnosis IBD, severe immunosuppression, or current gastrointestinal infection	3	Follow up rate 100%
Ge, 2011 (31)	China	Cases-only G x E interaction	Department of Rheumatology, First Affiliated Hospital, Anhui Medical University	No information	No information	N/A	No information
Sundström, 2011 (32)	Sweden	Case series	Department of Rheumatology, County of Västerbotten	Patients with a registered ICD-10 M45.9 diagnosis of AS	No information	N/A	83%
Sundström, 2012 (33)	Sweden	Case series	Department of Rheumatology, University Hospital of Umeå	Patients diagnosed with AS and fulfilling the modified New York criteria, age 18–70 years	Pregnancy, lactation, use of lipid-lowering medication, treatment with dalteparin sodium, warfarin, or biological products	N/A	No information
Silva, 2014 (39)	Portugal	Case series	Rheumatology Department of Centro Hospitalar de Lisboa Ocidental, Hospital de Egas Moniz	No information	No information	N/A	No information
Sundström, 2014 (34)	Sweden	Case-control	Cases: Department of Rheumatology, County of Västerbotten Controls: VIP database	Cases: Patients diagnosed with AS and fulfilling the modified New York criteria, age 18–70 years Controls: Matched for age (±2.5 years), gender and date in VIP database	No information	N/A	89%
Taşpınar, 2014 (40)	Turkey	Case series	Department of Rheumatology and Department of Physical Medicine and Rehabilitation, Bezmiâlem Vakif University, Istanbul	No information	No information	N/A	No information

AS: ankylosing spondylitis; RCT: Randomised clinical trial; BASDAI: Bath Ankylosing Disease Activity Index; ESR: Erythrocyte Sedimentation Rate; UCDAI: Ulcerative Colitis Disease Activity Index ; N/A: Not applicable; BASFI: Bath Ankylosing Functional Index; VIP: Västerbotten Intervention Programme; G x E: Gene x Environment interaction; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; ICD-10: International Classification of Diseases, Tenth Revision; NASS: National Ankylosing Spondylitis Society;

Appendix 2. Description of participants

First author, Publication year	Study size	Females, n (%)	Age, years	Disease duration, years	AS Diagnostic criteria	Assessment of diet	Measure of disease activity
Haugen, 1991 (25)	87	30 (34%)	Median 36 (Range 18-62)	Median 9 (Range 0-35)	Hospital diagnosis	Questionnaire (influence of diet on symptoms; reproducibility assessed)	Aggravation of symptoms (0-10cm VAS); NSAIDs /corticosteroids intake
Appelboom, 1994 (35)	25	No information	No information	No information	ESSG	Intervention	Change in comparison to baseline (worse, no change, better)
Ebringer, 1996 (37)	36	No information	No information	No information	Hospital diagnosis	Intervention	ESR
Claudepierre, 1998 (26)	293	107 (36.5)	Mean 40.3 (SD 13.5)	Mean 10.7 (SD 9.9)	ESSG or Amor	Interview with a dietician	BASDAI
Ebringer, 2006 (38)	74	No information	No information	No information	Hospital diagnosis	Intervention	ESR
Sundström, 2006 (27)	24	9 (37.5)	Median 49 (Range 33-69)	Median 19 (IQR 15)	Diagnosis of AS by a rheumatologist	Intervention	ESR, BASDAI, BASFI, analgesics and NSAIDs intake
Brophy 2008 (28)	147	40 (30%)	PI Mean 42.7 (SD 12.7) Pr Mean 44.8 (SD 12.1)	PI Mean 20.3 (SD 13.4) Pr Mean 20.3 (SD 13.2)	Diagnosis of SpA made by a rheumatologist and confirmed by x-ray or magnetic resonance scan	Intervention	Global wellbeing (0-10), disease activity (0-10), function (0-10); 10=the worst

Chatfield, 2009 (29)	75	24 (32.0)	Mean 48.2 (SD 12.9)	Mean 21.8 (SD 12.2)	Modified New York	Telephone survey (open-ended questions on avoidance of foods, special diets, CAM in the past 3 months	BASDAI, BASFI, ASQoL, BASG, ESR, CRP
Sanges, 2009 (36)	18	10 (56%)	Mean 49	No information	Hospital diagnosis	Intervention	BASFI, BASDAI, VAS, CRP, ESR
Jenks 2010 (30)	63	23 (37%)	Mean 43.3 (range 19-76)	Mean 8.9 (range 1-53)	ESSG	Intervention	BASFI, BASDAI, ASAS, ASAS20, CRP, fatigue, global assessment VAS, ASQoL
Ge, 2011 (31)	150	28 (19%)	Mean 29.9 (SD 9.61)	No information	Modified New York	Questionnaire (yes/no questions)	N/A
Sundström, 2011 (32)	111	27 (24%)	Mean 49.5 (SD 10.4)	Mean 26.9 (SD 10.5)	Modified New York	Questionnaire (validated)	BASDAI, BASFI, Aggravation of symptoms
Sundström, 2012 (33)	66	15 (22.7)	Mean 47.7 (SD 10.0)	Mean 17.0 (SD 10.8)	Modified New York	Questionnaire (validated)	BASDAI, BASFI, BASG, SF-36, CRP
Silva, 2014 (39)	12	3 (25%)	No information	No information	No information	Food diary (5 consecutive days)	BASDAI, BASFI, BASG, SF-36, CRP, ESR
Sundström, 2014 (34)	88 351	20 (23%)	Cases: Median 50 (Range 40-60)	No information	Modified New York	Questionnaire (validated)	N/A
Taşpınar, 2014 (40)	100	No information	No information	No information	ESSG, ASAS, Amor	Interview	BASDAI

VAS: Visual Analogue Scale; ESSG: European Spondylarthropathy Study Group; NSAIDs: nonsteroidal anti-inflammatory drugs; ESR: Erythrocyte Sedimentation Rate; BASDAI: Bath Ankylosing Disease Activity Index; BASFI: Bath Ankylosing Functional Index; SpA: Spondyloarthritis; CAM: Complementary and alternative medicines; Pr: Probiotics; Pl: Placebo; ASQoL: AS Quality of Life; CRP: C-reactive protein; BASG: Bath AS Patient Global Score; ASAS : Assessment of Spondyloarthritis International Society; SF-36: 36-Item Short Form Health Survey; AS: ankylosing spondylitis;

Appendix 3. Availability of dietary information in the studies included in the review

	Haugen, 1991 (25)	**Appelboom, 1994** (35)	**Ebringer, 1996** (37)	**Claudepierre, 1998** (26)	**Ebringer, 2006** (38)	**Sundström, 2006** (27)	**Brophy, 2008** (28)	**Chatfield, 2009** (29)	**Sanges, 2009** (36)	**Jenks, 2010** (30)	**Ge, 2011** (31)	**Sundström, 2011** (32)	**Sundström, 2012** (33)	**Silva, 2014** (39)	**Sundström, 2014** (34)	**Taşpınar, 2014** (40)	**Total**
Diet																	
Dairy		✓		✓								✓			✓	✓	5
Foods high in starch			✓	✓	✓							✓		✓		✓	6
Fish												✓			✓		2
Fruit and vegetables											✓	✓			✓		3
Meat and meat products				✓							✓	✓			✓		4
Cooking oil											✓						1
Salt consumption											✓					✓	2
Canned food				✓													1
Frozen foods				✓													1
Fast food																✓	1
Meals taken out of home				✓													1
Believe that diet influences symptoms	✓																1
Foods that aggravate symptoms	✓											✓					2
Fasting	✓																1
Specific diet	✓																1
Nutrients																	
Energy												✓	✓		✓		3
Fat												✓	✓		✓		3
Protein												✓	✓		✓		3
Starch				✓													1
Carbohydrate												✓	✓		✓		2
Fatty acids												✓	✓		✓		2
Fibre												✓			✓		2
Dietary complementary and alternative medicines (CAM)																	
Probiotics							✓		✓	✓							3
Fish oil						✓		✓				✓					3
Other CAM								✓				✓					2

CAM: Complementary and alternative medicines;

Appendix 4. Quality assessment of studies reporting case series

Criteria	First author, publication year							
	Haugen, 1991 (25)	Claudepierre, 1998 (26)	Chatfield, 2009 (29)	Ge, 2011 (31)	Sundström, 2011 (32)	Sundström, 2012 (33)	Silva, 2014 (39)	Taşpınar, 2014 (40)
State specific objectives, including any pre-specified hypotheses	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes
Study population is clearly and fully described, including a case definition, inclusion and exclusion criteria	No	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell
Were the cases consecutive?	Yes	Yes	Can't tell	No	Can't tell	Can't tell	Can't tell	Can't tell
The sample of cases is representative with regard to the population to which the findings are be referred	Can't tell	Can't tell	No	Can't tell	Can't tell	Can't tell	No	Can't tell
The sample size is based on pre-study considerations of statistical power	Can't tell	No	Can't tell	No	No	No	Can't tell	Can't tell
Participation rate is reported	Yes	Yes	No	Yes	Yes	No	No	No
The outcome measures are clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
The exposure measurements (e.g. questionnaires) are likely to be valid and reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Confidence intervals are provided	No	No	Yes	Yes	No	No	No	No
The potential confounders are identified and taken into account in the design and analysis.	No	No	No	No	No	No	Yes	No
Laboratory methods are described, including source and storage of DNA, genotyping methods and platforms, error rates ad call rates.	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Not applicable

Appendix 5. Quality assessment of uncontrolled treatment outcome studies

Criteria	First author, publication year			
	Appelboom, 1994 (35)	Ebringer, 1996 (37)	Ebringer, 2006 (38)	Sanges, 2009 (36)
State specific objectives, including any pre-specified hypotheses	Yes	No	No	Yes
The study population is clearly and fully described, including a case definition, inclusion and exclusion criteria	Yes	No	No	No
The sample size was based on pre-study considerations of statistical power	Can't tell	Can't tell	No	Can't tell
The baseline participation rate is reported	No	No	No	No
The follow up (or dropout) rate is reported	No	No	No	No
Comparison is made between full participants and those lost to follow up	No	No	No	No
The outcome measures are clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	Yes	No	Yes
Confidence intervals are provided	No	No	No	No
The potential confounders are identified and taken into account in the design and analysis.	Yes	No	No	No
Compliance assessment	Questions to participants (poor, questionable, good)	Self-report (minority of patients reported difficulty to adhere to diet; support was available)	Can't tell	Can't tell

Appendix 6. Quality assessment of case-control studies

Criteria	First author, publication year
	Sundström, 2014 (34)
State specific objectives, including any pre-specified hypotheses	Yes
The case population is clearly and fully described, including a case definition, inclusion and exclusion criteria	Yes
Cases are clearly differentiated from controls.	Yes
Sample size is based on pre-study considerations of statistical power?	No
The cases and controls are taken from comparable populations	Yes
The same exclusion criteria are used for both cases and controls	Yes
Participation rate for both cases and controls is reported	No (cases only)
Comparison is made between participants and non-participants to establish their similarities or differences.	Yes
Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment	Not mentioned
Exposure status is measured in a standard, valid and reliable way	Yes
The main potential confounders are identified and taken into account in the design and analysis	Yes
Confidence intervals are provided	No

Appendix 7. Quality assessment of randomised clinical trials (RCTs)

Criteria	First author, publication year		
	Sundström, 2006 (27)	Brophy 2008 (28)	Jenks 2010 (30)
State specific objectives, including any pre-specified hypotheses	Yes	Yes	Yes
The study population is clearly and fully described, including a case definition, inclusion and exclusion criteria	Yes	Yes	Yes
The sample size is based on pre-study considerations of statistical power	No	Yes	Yes
The assignment of subjects to treatment groups is random	Yes	Yes	Yes
An adequate concealment method was used	Can't tell	Yes	Yes
The design keeps subjects and investigators 'blind' about treatment allocation	Can't tell	Yes	Yes
The treatment and control groups are similar at the start of the trial	Yes	Yes	Yes
The follow up (or dropout) rate is reported	Yes	Yes	Yes
The outcome measures are clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	Yes	Yes
Intention to treat analysis was conducted	No	Yes	Yes
Confidence intervals are provided	No	Yes	Yes
Compliance assessment	Participants counted the remaining capsules	Participants reported on the number of study capsules that they had taken during the previous week	Participants returned all study drug containers at weeks 4, 8 and 12; Containers were weighted to document compliance

Appendix 8. Methods used for statistical data analysis

First author, Publication year	Statistical methods used	Confounding factors considered
Haugen, 1991 (25)	Percent;	Information was available on age, gender and disease duration but no report on relationship with disease symptoms
Appelboom, 1994 (35)	Percent; Fisher's exact test; Chi-square test	No association between response and age, gender, duration of disease, HLA-B27, axial versus peripheral involvement, enthesopathies, sacroiliitis, intestinal, genitourinary or cutaneous symptoms.
Ebringer, 1996 (37)	Mean; SE; t-test	No information
Claudepierre, 1998 (26)	Mean; SD; Median; rage; correlation; Kruskall-Wallis test; Mann-Whitney U test; Linear regression	Age at disease onset, gender, HLA-B27 status, disease duration
Ebringer, 2006 (38)	No information	No information
Sundström, 2006 (27)	Median; IQR; Mann-Whitney U test; Fisher exact test; Wilcoxon signed rank test	RCT (baseline information was collected on age, gender, age at onset of symptoms, disease duration, time to diagnosis)
Brophy 2008 (28)	Percent; Mean; SD; General linear model adjusted or age, gender, disease duration and baseline levels	RCT (baseline information was collected on age, gender, disease duration, iritis, inflammatory bowel disease, medication)
Chatfield, 2009 (29)	Mean; SD; Percent; t-test; chi-square test; Multivariate logistic regression	Age, gender, HLA-B27 status, disease duration, delay in diagnosis, family history, peripheral arthritis, smoking, education, employment, medication
Sanges, 2009 (36)	Mean; SD; t-test	Age, gender
Jenks 2010 (30)	Mean; SD; Percent; ANCOVA	RCT (baseline information was collected on age, gender, disease duration, HLA-B27 status, history of anterior uveitis, history of psoriasis, medication)
Ge, 2011 (31)	OR; 95% CI; Logistic regression; P-value for interaction	Information was available on age, gender, HLA-B27 (all positive), smoking, medical history
Sundström, 2011 (32)	Percent; Mean; SD; Mann-Whitney U test; Fisher exact test; Spearman's rank correlation; multiple logistic regression	Age, gender, disease duration, BMI, physical activity
Sundström, 2012 (33)	Percent; Mean; SD; Mann-Whitney U test; Fisher exact test; Spearman's rank correlation; Pearson correlation; multiple linear regression	Age, gender, disease duration, BMI, physical activity, smoking
Silva, 2014 (39)	Mean; SD; Pearson correlation; Linear regression	Age, gender, medication, BMI
Sundström, 2014 (34)	Spearman's rank correlation; conditional logistic regression; multiple linear regression	Age, gender, BMI, physical activity, education, smoking; medication; medical history
Taşpınar, 2014 (40)	Correlation	Age, gender, disease duration, smoking, medical history

SD: Standard deviation; SE: Standard error; OR: Odds ratio; CI: Confidence interval; ANCOVA: Analysis of covariance; IQR: Interquartile range; HLA-B27: human leukocyte antigen B27; BMI: Body mass index

Appendix 9. Summary of evidence on relationship between high-starch food and AS

First author, publication year	Type of publication	Type of study	N of participants (duration of follow up)	Exposure	Outcomes	Results/Conclusion
Ebringer 1996 (37)	Summary in review paper	Uncontrolled treatment outcome	36 (9 months)	Low starch diet (reduced intake of bread, potatoes, chips, rice, spaghetti, cereals, cakes, biscuits)	ESR, symptom severity, requirement for NSAIDs	- Significant reduction in ESR levels from mean (SE) of 38 (3) mm/hr at baseline to 24 (2) mm/hr at follow up (P<0.001) - Majority of the participants reported that the severity of symptoms declined and in some cases disappeared (no precise figures were reported). - Some patients noticed decrease in requirement for NSAIDs (no precise figures were reported)
Ebringer 2006 (38)	Summary in review paper	Uncontrolled treatment outcome	74 (10 months)	Low starch, high protein, high vegetable and fruit diet	ESR	Decrease in ESR (no precise figures were reported)
Claudepierre 1998 (26)	Full text	Case series	293	Consumption of food high in starch content (i.e. bread, pasta, rice, potatoes, rusk, maize, beans, peas, pizza, quiches, couscous) Weekly starch consumption	BASDAI	No association (no precise figures were reported)
Sundström 2011 (32)	Full text	Case series	111	Food rich in flour	Aggravated arthralgia or AS symptoms	2 (1.8%) patients reported that they experienced aggravation of symptoms associated with food rich in flour
Silva 2014 (39)	Conference abstract	Case series	12	Average daily starch intake	BASDAI, BASFI, BASG, SF-36, CRP, ESR	- Significant association with the BASDAI (p<0.05), BASFI (p<0.05), and BASG (p<0.05); The liner regression showed an increase of 3%, 3.9% and 2.9% in BASDAI, BASFI and BASG scores, respectively, by milligram of ingested starch - No association with the SF-36, CRP or ESR (no precise figures were reported)
Taşpınar 2014 (40)	Conference abstract	Case series	100	Consumption of wheat, cereal, whole wheat bread, white bread	BASDAI	No association (p>0.05) (no precise figures were reported)

AS: ankylosing spondylitis; ESR: Erythrocyte Sedimentation Rate; NSAIDs: nonsteroidal anti-inflammatory drugs; SE: Standard error; BASDAI: Bath Ankylosing Disease Activity Index; BASFI: Bath Ankylosing Functional Index; BASG: Bath AS Patient Global Score; SF-36: 36-Item Short Form Health Survey; CRP: C-reactive protein;

Appendix 10. Summary of evidence on relationship between dairy products and AS

First author, publication year	Type of publication	Type of study	N of participants (duration of follow up)	Exposure	Outcomes	Results/Conclusion
Appelboom 1994 (35)	Letter	Uncontrolled treatment outcome	25 (9 months)	Diet that excluded dairy products (milk, cheese, yoghurt, ice cream and butter),	Self-reported therapeutic effect, NSAID therapy	- 52% reported good and 16% a moderate improvement at 6 weeks follow up. - 62% of 13 "good" responders could discontinue NSAID therapy at 6 weeks follow up. - 80% of 15 patients were still satisfied and kept up the diet at 3 months, - 100% of 10 patients were still satisfied and kept up the diet at 6 months - 89% of 9 patients were still satisfied and kept up the diet at 9 months.
Sundström 2014 (34)	Full text	Case-control	77 AS 307 Controls	Milk and soured milk	AS	No significant difference between cases and controls. Median (IQR) serving per week in AS cases: 13 (7.5-18.1), controls: 11 (7.0-18.7) (P=0.61).
Sundström 2011 (32)	Full text	Case series	111	Milk and soured milk	BASDAI	No correlation (no precise figures were reported)
Claudepierre 1998 (26)	Full text	Case series	293	Dairy	BASDAI	No association (no precise figures were reported)
Taşpınar 2014 (40)	Conference abstract	Case series	100	Consumption of milk, yogurt, cheese, butter, margarine	BASDAI	No association (p>0.05) (no precise figures were reported)

AS: ankylosing spondylitis; IQR: Interquartile range; BASDAI: Bath Ankylosing Disease Activity Index; NSAIDs: nonsteroidal anti-inflammatory drugs;

Appendix 11. Summary of evidence on relationship between consumption of fish and fish oil and AS

First author, publication year	Type of publication	Type of study	N of participants (duration of follow up)	Exposure	Outcomes	Results/Conclusion
Sundström 2006 (27)	Full text	RCT	24 (baseline); 18 (follow up) (21 weeks)	High- versus low-dose fish oil	BASDAI, BASFI, ESR, medication requirement	No statistically significant difference; a trend towards a larger decrease from baseline in BASDAI was seen in the high-dose group (estimated from publication mean 1.4) compared to low-dose group (mean 0.57) (p=0.145); Trend towards decreased symptoms in the high-dose group according to patients' assessment of the effect of supplementation (P=0.102)
Sundström 2011 (32)	Full text	Case series	111	Fish consumption, use of omega-3 supplements in the past 2 weeks, omega-3 fatty acids as % of energy intake	BASDAI	No correlation (no precise figures were reported); 13 (12%) used pmega-3 supplements (median intake 1g/day, range 0.5-6.0)
Sundström 2014 (34)	Full text	Case-control	77 AS 307 Controls	Fish consumption	AS	No significant difference between cases and controls. Median (IQR) serving per week in AS cases: 1.6 (1.0-2.1), controls: 1.6 (0.6-2.1) (P=0.49).

AS: ankylosing spondylitis; IQR: Interquartile range; BASDAI: Bath Ankylosing Disease Activity Index; BASFI: Bath Ankylosing Functional Index; ESR: Erythrocyte Sedimentation Rate;

Appendix 12. Summary of evidence on relationship between consumption of fruit and vegetables and AS

First author, publication year	Type of publication	Type of study	N of participants	Exposure	Outcomes	Results/Conclusion
Ge 2011 (31)	Full text	Case series	150	Current vegetable consumption (frequency)	AS	OR (95% CI) for interaction between IL-1F7 gene (rs3811047) and vegetable consumption (Reference category: Less than six times per week) Once per day 0.311 (0.063–1.533) P=0.151 2–3 times per day 0.375 (0.079–1.778) P=0.217 More than three times per day 0.067 (0.004–1.116) P=0.060
Sundström 2011 (32)	Full text	Case series	111	Vegetables and fruits (servings per month)	Aggravated arthralgia or AS symptoms	2 (1.8%) patients reported that they experienced aggravation of symptoms associated with vegetables/fruits
Sundström 2014 (34)	Full text	Case-control	77 AS 307 Controls	Vegetables and fruits (servings per week)	AS	No significant difference between cases and controls. Median (IQR) serving of vegetables per week in AS cases: 7.6 (6.0-14.4), controls: 7.6 (4.5-14.7) (P=0.57); Median (IQR) serving of fruits per week in AS cases: 8.0 (4.1-14.0), controls: 7.6 (3.6-12.9) (P=0.80)

AS: ankylosing spondylitis ; OR: Odds ratio; CI: Confidence interval; IQR: Interquartile range;

Appendix 13. Summary of evidence on relationship between consumption of meat and meat products and AS

First author, publication year	Type of publication	Type of study	N of participants	Exposure	Outcomes	Results/Conclusion
Claudepierre 1998 (26)	Full text	Case series	293	Consumption of delicatessen food	BASDAI	No association (no precise figures were reported)
Ge 2011 (31)	Full text	Case series	150	Meat products consumption (type)	AS	OR (95% CI) for interaction between IL-1F7 gene (rs3811047) and meat products consumption (reference category: Fat) Fat and lean 1.793 (0.182–17.651) P=0.617 Lean 1.351 (0.144–12.636) P=0.792
Sundström 2011 (32)	Full text	Case series	111	Meat and meat products (servings per month)	BASDAI	No correlation (no precise figures were reported)
Sundström 2014 (34)	Full text	Case-control	77 AS 307 Controls	Meat and meat products (servings per week)	AS	No significant difference between cases and controls. Median (IQR) serving per week in AS cases: 5.6 (4.2-7.0), controls: 5.6 (4.3-6.7) (P=0.68).

AS: ankylosing spondylitis; IQR: Interquartile range; BASDAI: Bath Ankylosing Disease Activity Index;

Appendix 14. Summary of evidence on relationship between consumption of convenience food, cooking oil and salt and AS

First author, publication year	Type of publication	Type of study	N of participants	Exposure	Outcomes	Results/Conclusion
Claudepierre 1998 (26)	Full text	Case series	293	Consumption of canned food, frozen food; Number of meals taken out of home (per week)	BASDAI	No association (no precise figures were reported) with canned or frozen food; Mean (SD) BASDAI 5.1 (2.1) for patients eating out ≤2 per week and 4.1 (2.1) for patients eating out >2 per week (P<0.001)
Ge 2011 (31)	Full text	Case series	150	Cooking oil and salt consumption	AS	OR (95% CI) for interaction between IL-1F7 gene (rs3811047) and cooking oil (reference category: Main plant fats) Absolute plant fats 2.02 (0.732–5.575) P=0.175 Half plants-half animal fats 4.273 (1.590-11.479) P=0.004 Animal fats 0.306 (0.081-1.153) P=0.071 OR (95% CI) for interaction between IL-1F7 gene (rs3811047) and salt consumption (reference category: Light) Moderate 1.0 (0.355–2.818) P=1.000 Salty 1.523 (0.557–4.163) P=0.413
Taşpınar 2014 (40)	Conference abstract	Case series	100	Consumption of fast food and salt	BASDAI	No association (p>0.05) (no precise figures were reported)

AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Disease Activity Index; OR: Odds ratio;

Appendix 15. Summary of evidence on relationship between probiotic and other CAM supplementation and AS

First author, publication year	Type of publication	Type of study	N of participants (duration of follow up)	Exposure	Outcomes #	Estimated effect
Brophy 2008 (28)	Full text	RCT	147 (baseline) 134 (follow up) (12 weeks)	Probiotic group: 10 g lyophilized powder (capsule) containing live bacteria: *Lactobacillus salivarius* (CUL61) 6.25 × 109 cfu (colony forming units), *Lactobacilllus paracasei* (CUL08) 1.25 × 109cfu, *Bifidobacterium infantis* (CUL34) 1.25 × 109 cfu *Bifidobacterium bifidum* (CUL20) 1.25 × 109 cfu) Placebo group: 10 g maltodextrin capsule *Dose*: One capsule by mouth daily	# 0–10 scale (10 is worst) Global wellbeing Disease activity Function	Change in scale (95% CI); a positive value indicates a worsening in condition 0.16 (-0.16, 0.93) 0.20 (-0.47, 0.86) -0.04 (-0.50, 0.43)
Sanges, 2009 (36)	Letter	Uncontrolled treatment outcome	18 (4 weeks)	*Lactobacillus Acidophilus and Lactobacillus salivarius, 2 billions* Dose: Daily in two divided doses	BASDAI BASFI VAS CRP ESR	Mean (SD): Baseline; Follow up 5.8 (1.5); 4 (1.8) P< 0.05 33.6 (10); 28.6(6.3) 58.1 (16.8); 41.5 (14.3) P< 0.05 25.2 (11); 19.8 (6.4) 28 (11.6); 22.5 (7.1)
Jenks 2010 (30)	Full text	RCT	63 (baseline) 62 (follow up) (12 weeks)	Probiotic group: *Streptococcus salivarius* K12 (1 x 108 cfu/g), *Bifidobacterium lactis* LAFTI B94 (4 x 108 cfu/g), and *Lactobacillus acidophilus* LAFTI L10 (4 x 108 cfu/g) (5.5% of the weight of the powder composition). The remainder of the formulation consisted of the excipient ingredients, identical to placebo. Placebo group: Powder of glucidex 37.6%, trehalose 56.49%, and vanilla flavour 0.43% identical in appearance, taste, and texture to the active probiotic treatment. *Dose*: One level spoonful (approximately 0.8 g) by mouth twice daily	# 0–10 scale (10 is worst) Global VAS BASDAI BASFI Pain VAS CRP ASQoL	Change in scale (95% CI); a positive value indicates a worsening in condition -0.4 (-1.4, 0.7) -0.6 (-1.6, 0.3) -0.1 (-0.7, 0.6) 0.2 (-0.8, 1.1) -3.5 (-7.8, 0.8) -0.5 (-2.0, 1.1)
Chatfield, 2009 (29)	Full text	Case series	75	Current CAM use (within past 3 months) including dietary (avoidance or inclusion of specific foods or supplements)	ESR CRP BASDAI BASFI ASQoL	Mean (SD) in users / non-users 23.9 (23.4) / 27.4 (17.7) P=0.61 21.8 (24.9) / 31.5 (48.8) P=0.29 2.9 (2.4) / 3.2 (2.8) P=0.68 5.3 (2.9) / 5.6 (2.4) P=0.73 9.9 (5.3) / 8.2 (4.6) P=0.31

					BASG	5.8 (2.6) / 5.2 (2.8) P=0.46
Sundström 2011 (32)	Full text	Case series	111	Herbal products, multivitamins and other food supplements in the past 2 weeks	Prevalence of use	32 (29%) reported consumption; the most common were omega-3 (13), multivitamin and/or mineral (12) and iron (4)

AS: ankylosing spondylitis; RCT: Randomised Clinical Trial; SD: Standard Deviation; CI: Confidence Interval; BASDAI: Bath Ankylosing Disease Activity Index; ASQoL: AS Quality of Life; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; SF-36: 36-Item Short Form Health Survey; -BASDAI: Bath Ankylosing Disease Activity Index; BASFI: Bath Ankylosing Functional Index; BASG: Bath AS Patient Global Score; VAS: Visual Analogue Scale

Appendix 16. Summary of evidence on relationship between specific diet and AS

First author, publication year	Type of publication	Type of study	N of participants	Exposure	Outcomes	Results/Conclusion
Haugen, 1991 (25)	Full text	Case series	87	Specific diet	Self-reported symptoms	68 (78%) believed that diet influenced disease symptoms; 29 (43%) of these believed that diet had great influence (VAS >5); 14 (16%) had previously fasted on their own initiative to ameliorate disease symptoms and the majority reported less pain, less stiffness and less joint swelling; 19 (22%) tried dietary therapy in an attempt to alleviate symptoms; 36% reported increased swelling of the joint associated with certain types of food (no information available)
Sundström 2011 (32)	Full text	Case series	111	Type of food	Self-reported symptoms	7 (6%) reported that they experienced aggravated arthralgia or AS symptoms associated with particular foodstuff;

AS: ankylosing spondylitis; VAS: Visual Analogies Scale

Appendix 17. Summary of evidence on relationship between nutrient intake and AS

First author, publication year	Type of publication	Type of study	N of participants	Exposure	Outcomes	Results/Conclusion
Sundström 2011 (32)	Full text	Case series	111	Energy intake (kJ); Protein, %E Carbohydrate, %E Fibre, grams Fat, %E Saturated fats, %E	BASDAI	No correlation (no precise figures were reported) Women only: rs=−0.43, P<0.05 rs=−0.50, P<0.01
Sundström, 2012 (33)	Full text	Case series	66	 Protein, %E Carbohydrate, %E Fat, %E	BASDAI, ESR, hsCRP	(BASDAI, ESR, hsCRP respectively); P>0.05 rs= –0.17, rs=–0.06, rs= 0.01 rs= –0.12, rs= 0.22, rs= 0.10 rs= 0.10, rs= –0.21, rs= 0.04
Sundström 2014 (34)	Full text	Case-control	77 AS 307 Controls	 Energy intake (kcal) Protein, E% Carbohydrate, E% Fat, E% Fibre/energy, grams/1000 kcal	AS	Mean (SD) Cases: 1940 (503), Controls: 1819 (510) p<0.05 Cases: 15 (2.0), Controls: 15 (2.2) p=0.73 Cases: 48 (5.8), Controls: 47 (6.5) p=0.11 Cases: 34 (5.6), Controls: 35 (6.2) p=0.07 Cases: 11 (3.0), Controls: 11 (3.3) p=0.85

%E: % of energy intake; AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Disease Activity Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; SD: Standard Deviation

Appendix 18. Summary of evidence on relationship between dietary fatty acids intake and AS

First author, publication year	Type of publication	Type of study	N of participants	Exposure	Outcomes	Results/Conclusion
Sundström 2011 (32)	Full text	Case series	111	Saturated fatty acids, %E Polyunsaturated fatty acids, %E Long-chain omega-3 fatty acids, %E Omega-3 fatty acids, %E	BASDAI	No correlation (no precise figures were reported)
Sundström, 2012 (33)	Full text	Case series	66	Saturated fatty acids, %E Linoleic acid, %E Alpha-linolenic acid, %E Polyunsaturated fatty acids, %E Long-chain omega-3 fatty acids, %E	BASDAI, ESR, hsCRP	(BASDAI, ESR, hsCRP respectively) rs= –0.01, rs= 0.00, rs= 0.10 rs= 0.11, rs= –0.24, rs= –0.10 rs= 0.06, rs= –0.22, rs= 0.00 rs= 0.10, rs= –0.25 (P<0.005), rs= –0.11 rs= 0.06, rs= –0.27 (P<0.005), rs= –0.17
Sundström 2014 (34)	Full text	Case-control	77 AS 307 Controls	Saturated fatty acids, E% Mono-unsaturated fatty acids, E% Polyunsaturated fatty acids, E% Linoleic acid, E% Alpha-linolenic acid, E% Long-chain omega-3 fatty acids, E%	AS	Mean (SD) Cases: 14 (2.9), Controls: 14 (3.2) p=0.26 Cases: 12 (2.2), Controls:12 (2.3) p=0.07 Cases: 5.7 (1.6), Controls: 6.0 (2.1) p=0.26 Cases: 4.2 (1.4), Controls: 4.4 (1.8) p=0.47 Cases: 0.8 (0.2), Controls: 0.8 (0.3) p=0.52 Cases: 0.09 (0.06), Controls: 0.11 (0.08) p=0.16

%E: % of energy intake; AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Disease Activity Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; SD: Standard Deviation